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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,758	04/24/2001	Olga Bandman	PF-0163-2 DIV	6839

7590 03/13/2003

Legal Department
Incyte Genomics Inc
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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/13/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,758	BANDMAN ET AL	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3-12 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed 12/23/2002 (paper no 11) is acknowledged and entered into the record. The Furness Declaration filed 12/23/2003 (paper no 12) is also acknowledged.

2. Claims 1-20 are pending in the instant application. Claims 3-12 and 15-20 are withdrawn from further consideration as being drawn to a non-elected subject matter.

3. Therefore, claims 1-2 and 13-14 are examined on the record.

Claim Rejections Withdrawn- 35 USC § 112, 2nd paragraph

4. The rejection of claims 1,2, 13 and 14 under 35 USC 112, 2nd paragraph as being indefinite is withdrawn in view of the amendments set forth by the applicant.

Claim Rejections Maintained- 35 USC § 101

5. The rejection of claims 1-2 and 13-14 under 35 U.S.C.§101, because the claimed invention is not supported by a specific, substantial, or credible utility, is **maintained**, for the reasons of record.

Applicant argues that the rejection was improper and that the invention is indeed supported by a patentable utility and/or a utility well known to one of skill in the art. Applicant further argues that HSEBP has a variety of utilities, in particular expression profiling, diagnosis of conditions or diseases, toxicology testing and drug discovery. Applicant also argues that the fact that HSEBP is similar to another already known protein is in itself proof that the instant invention has utility. In addition, applicant argues that there is indeed direct proof of utility, through the declaration of Lars Michael Furness, wherein Mr. Furness discloses practical uses of the instant invention (gene

protein expression monitoring (2D gels and western blotting)), and how the instant invention is useful for evaluating toxicity of drug candidates. Further still, applicant argues that law does not require knowledge of biological function to prove utility. Applicant's arguments are not found persuasive for the following reasons.

The assertion that the disclosed HSEBPs have biological activities similar to known human selenium-binding proteins is not credible in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full

paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in

Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of human synthase activity.

The specification does not support a credible, specific and substantial utility regarding the claimed polypeptide and fragments/variants thereof for purposes unrelated to the asserted biological activity. For example, the specification asserts that the claimed polypeptide has fatty acid synthase activity based solely on the structural similarity to other FAS proteins. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptide. Also, the specification does not predict whether the claimed polypeptide would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control. The specification contains assertions that the claimed

polypeptide can be used in gene expression monitoring assays, which are used in the art for drug development and toxicology studies. However, without a disclosure of a particular disease state in which the claimed polypeptides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean.

Applicant presents the Furness Declaration as direct proof of the utility of the instant invention that "direct proof' (referring to the Furness Declaration) of the utility of the claimed invention was submitted, April 22, 2002 (paper no. 12). A specification can meet the legal requirements of utility and enablement for a new polypeptide as long as the specification discloses a credible, specific and substantial asserted utility for the new polypeptide or a well-established utility for the claimed polypeptide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polypeptide is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the claimed polypeptide. The claimed polypeptide in the hypothetical example would not be rejected under 35 USC 101 and 112, first paragraph, as it has utility and is enabled as a colon cancer marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polypeptides are structurally related to cell junction proteins and hypothesizes that the claimed polypeptides are involved in proliferative disorders, but the expression of the claimed polypeptides in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no disclosure that the claimed polypeptides are expressed at altered levels or forms in any

specific, diseased tissue. It is noted that the instant application was filed March 16, 2000. No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue. Also no evidence has been brought forth that the claimed polypeptides are in fact fatty acid synthase proteins.

. The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claim Rejections Maintained- 35 USC § 112,1st paragraph

6. Claims 1, 21, and 33 rejected under 35 USC§112, 1st paragraph as lacking proper written description is maintained for the reasons of record. Applicants arguments have been carefully considered but are not found persuasive for the following reasons. Applicant argues that SEQ ID No: 1 is fully disclosed in the specification and one of skill in the art would clearly understand a variant that was 96% homologous to SEQ ID No: 1. Although the examiner does not contend that this is true, in order to have proper written description of a sequence, the amino acid sequence itself is required (see *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.). Regarding immunologically active fragments, because the fragments themselves are not disclosed,

one of skill in the arts would not understand how to or what to screen. Potentially, the entire protein could be immunogenic given that enough of the protein fragments are administered to elicit a response. And lastly, one of skill in the art would be required to screen numerous parts of the protein to look for active fragments, because as disclosed in the specification, there are numerous motifs localized within the protein sequence. Because of the mere recitation of the fragments does not qualify as adequate written description, one of skill would not know where to begin to search for such active fragments.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
March 10, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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